# Addition of halogenoacetic esters to aldehydes and ketones in the presence of $Fe(CO)_5$

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The use of complex-forming solvents and variations in the reaction temperature made it possible to prepare α-halogeno β-hydroxy carboxylic esters upon addition of halogenoacetic esters to aldehydes and ketones promoted by iron pentacarbonyl.

**Key words:** Reformatsky reaction, iron pentacarbonyl, halogenoacetic esters, aldehydes, ketones, addition reaction.

Recently, considerable attention has been given to the development of new synthetic procedures for the formation of C—C bonds using reactions involving metals or their compounds in which the metals are in the lowest valence state. In this case, the addition reactions at the multiple bonds, in particular, at the C=C and C=O bonds, are of great importance.

Considerable advances in this field have been made owing to the use of $SmI_2$ as the reagent in combination with particular solvents and additives.[1] Previously, we have demonstrated for the first time that iron pentacarbonyl is an efficient promoter of the Reformatsky-type addition of α-halogeno carboxylic esters to aldehydes and ketones.[2,3] In these reactions, $CBrCl_3$, $Br_2$, or $I_2$ was used as the activating agent (see Ref. 3).

As part of our continuing studies, in the present work we investigated the effects of the temperature and the nature of the solvent on the course of the reaction.

It is known[4] that complex-forming solvents favor the Reformatsky-type addition under milder conditions and improve the selectivity of the processes. It is also significant that under the conditions which we have originally used (*i.e.*, in boiling benzene), methyl bromoacetate (**1**) did not enter into the reaction and polyhalogenoacetic esters reacted with aldehydes and ketones to form acrylic acid derivatives without intermediate formation of esters of hydroxy acids.

We found that the addition of bromoester **1** to benzaldehyde (**2a**) and butyl methyl ketone (**2b**) yielding esters of β-hydroxy acids **3a,b** proceeded rather successfully only at 130 °C (boiling in chlorobenzene).

**Scheme 1**

$$\underset{\mathbf{1}}{CH_2BrCOOMe} + \underset{\mathbf{2a,b}}{R^1R^2C{=}O} \longrightarrow \underset{\mathbf{3a,b}}{R^1R^2C(OH)CH_2COOMe}$$

**a:** $R^1$ = Ph, $R^2$ = H

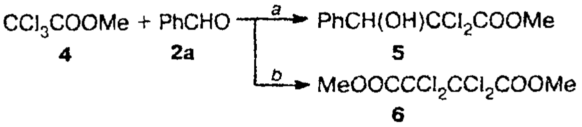
**b:** $R^1$ = Me, $R^2$ = $Bu^n$

**Reagents and conditions:** $Fe(CO)_5$, $CBrCl_3$, $C_6H_5Cl$, 130 °C, 2—4 h.

The structures of products **3a,b** were confirmed by spectral methods.

Among the products of the reaction with benzaldehyde, methyl cinnamate was identified by GLC-mass spectrometry, which is additional evidence for the structure of hydroxy ester **3a**. The reaction with butyl methyl ketone yielded products of aldol and crotonic condensation, which were detected in the reaction mixture by GLC-mass spectrometry, along with ester **3b**. The reactions of trichloro- and dibromoacetic esters with compounds **2a,b** in DMF or HMPA at -20 °C afforded esters of β-hydroxy acids as the major products. These reactions did not proceed in other solvents (benzene, THF, or DMSO) at -20 °C. The reaction of methyl trichloroacetate (**4**) with benzaldehyde (**2a**) in DMF carried out at room temperature over 3 days afforded methyl 2,2-dichloro-3-hydroxy-3-phenylpropionate (**5**) and methyl 2-chloro-3-phenylacrylate (in a ratio of 4 : 1), whereas this reaction in HMPA gave dimethyl tetrachlorosuccinate (**6**) (Scheme 2).

**Scheme 2**



$$\underset{\mathbf{4}}{CCl_3COOMe} + \underset{\mathbf{2a}}{PhCHO} \xrightarrow{a} \underset{\mathbf{5}}{PhCH(OH)CCl_2COOMe}$$
$$\underset{\mathbf{4}}{CCl_3COOMe} + \underset{\mathbf{2a}}{PhCHO} \xrightarrow{b} \underset{\mathbf{6}}{MeOOCCCl_2CCl_2COOMe}$$

**Reagents and conditions:** *a.* $Fe(CO)_5$, DMF, -20 °C, 3 days; *b.* $Fe(CO)_5$, HMPA, -20 °C, 3 days.

At room temperature, the reaction of ester **4** with butyl methyl ketone did not proceed, while dibromoacetate (**7**) reacted with benzaldehyde (**2a**) and butyl methyl ketone (**2b**) only in HMPA (Scheme 3).

**Scheme 3**

$$\underset{\mathbf{7}}{CHBr_2COOMe} + \mathbf{2a,b} \longrightarrow \underset{\mathbf{8}}{R^1R^2C(OH)CHBrCOOMe}$$

**Reagents and conditions:** $Fe(CO)_5$, HMPA, -20 °C, 3 days.

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To summarize, esters of β-hydroxy acids were prepared for the first time by the Reformatsky-type addition of polyhalogenoacetic esters, which was achieved by performing the synthesis in DMF or HMPA at –20 °C. Previously, the reactions of this type afforded acrylic esters.

## Experimental

The mass spectra were recorded on a Finnigan MAT Magnum GLC-mass spectrometer; a 25-m column (Ultra-2); heating from 30 to 220 °C (2.5 deg $min^{-1}$); the $m/z$ values of the ions are given for the $^{35}Cl$ and $^{79}Br$ isotopes. The GLC analysis was carried out on an LKhM-80 chromatograph equipped with a steel column (1300×3 mm) with 15% SKTFT-50Kh on Chromaton N-AW; helium as the carrier gas (60 mL $min^{-1}$); a katharometer as the detector, the temperature programming mode from 50 to 250 °C (6 deg $min^{-1}$). The $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker WP-200 instrument (200 MHz) in $CDCl_3$ as the solvent; the chemical shifts (δ) are given relative to $Me_4Si$.

All organic reagents were purified by distillation; $Fe(CO)_5$ (Fluka; 97%) was used without additional purification.

**Methyl 3-hydroxy-3-phenylpropionate (3a).** A solution of bromoester **1** (0.75 g, 5 mmol), benzaldehyde **2a** (0.53 g, 5 mmol), $Fe(CO)_5$ (1.14 g, 6 mmol), and $CBrCl_3$ (0.01 g, 0.05 mmol) in chlorobenzene (5 mL) was refluxed for 4 h. Then the reaction mixture was treated with dilute HCl and extracted with benzene. The extract was dried with $Na_2SO_4$ and the solvent was distilled off. The reaction mixtures which were obtained after analogous runs (the total amount of **1** used was 12 mmol) were combined and distilled. Methyl 3-hydroxy-3-phenylpropionate (**3a**) was isolated in a yield of 0.9 g (41%): b.p. 130 °C (7 Torr), $n_D^{20}$ 1.5312, $d_4^{20}$ 1.1365. $^1H$ NMR, δ: 2.66—2.71 (m, 2 H, $CH_2$); 3.40 (br.s, 1 H, OH); 3.65 (s, 3 H, MeO); 5.08 (s, 1 H, CH); 7.34 (m, 5 H, Ph). The data of $^1H$ NMR spectroscopy of compound **3a** agree with the results published previously.[4] MS, $m/z$ ($I_{rel}$ (%)): 180 $[M]^{+\cdot}$ (37), 163 $[M - OH]^+$ (41), 121 (61), 107 (100 ), 77 (28). Methyl cinnamate was identified in the reaction mixture by GLC-mass spectrometry. MS, $m/z$ ($I_{rel}$ (%)): 162 $[M]^{+\cdot}$ (76), 131 $[M - MeO]^+$ (100), 103 (95), 77 (31).

**Methyl 3-hydroxy-3-methylheptanoate (3b).** A solution of bromoester **1** (0.15 g, 1 mmol), ketone **2b** (0.10 g, 1 mmol), $Fe(CO)_5$ (0.39 g, 2 mmol), and $CBrCl_3$ (0.01 g, 0.05 mmol) in chlorobenzene (1 mL) was refluxed for 2 h. The reaction mixture was worked up as described above. Then the unconsumed initial reagents were distilled off, and the reaction mixture was analyzed by GLC-mass spectrometry and NMR spectroscopy. Methyl 3-hydroxy-3-methylheptanoate (**3b**) was identified as the major reaction product. The yield was 31%. $^1H$ NMR, δ: 0.78 (t, 3 H, $\underline{Me}CH_2$, $J$ = 8 Hz); 1.10 (s, 3 H, MeC); 1.15—1.45 (m, 6 H, 3 $CH_2$); 1.98 (s, 2 H, $CH_2$); 3.57 (s, 3 H, MeO); 5.88 (br.s, 1 H, OH). The data of $^1H$ NMR spectroscopy of compound **3b** agree with the results published previously.[5] MS, $m/z$ ($I_{rel}$ (%)): 175 $[M + 1]^+$ (21), 157 $[M - OH]^+$ (100), 125 (18), 117 (31), 101 (23).

**Reaction of methyl trichloroacetate (4) with benzaldehyde.** *A.* In DMF. A solution of ester **4** (0.17 g, 1 mmol), benzaldehyde **2a** (0.10 g, 1 mmol), and $Fe(CO)_5$ (0.39 g, 2 mmol) in DMF (1 mL) was kept at –20 °C for 3 days. The reaction mixture was worked up as described above. Then the unconsumed initial reagents were distilled off, and methyl 2,2-dichloro-3-hydroxy-3-phenylpropionate (**5**) was identified by GLC-mass spectrometry and NMR spectroscopy. The yield was 29.5%. $^1H$ NMR, δ: 2.81 (br.s, 1 H, OH); 3.85 (s, 3 H, MeO); 5.47 (s, 1 H, CH); 7.36 (m, 5 H, Ph).

$^{13}C$ NMR, δ: 165.9 (COO); 85.8 ($CCl_2$); 78.2 (CH); 54.2 (MeO); 127.2, 127.8, 128.3, 128.6, 129.3, 135.2 (Ph). MS, $m/z$ ($I_{rel}$ (%)): 231 $[M - OH]^+$ (4), 107 (100), 77 (80), 59 (53). Methyl 2-chloro-3-phenylacrylate was also identified. The yield was 8%. MS, $m/z$ ($I_{rel}$ (%)): 196 $[M]^{+\cdot}$ (54), 161 $[M - Cl]^+$ (39), 102 (100), 77 (28).

*B.* In HMPA. A solution of ester **4** (0.17 g, 1 mmol), benzaldehyde **2a** (0.10 g, 1 mmol), and $Fe(CO)_5$ (0.39 g, 2 mmol) in HMPA (1 mL) was kept at –20 °C for 3 days. Then the reaction mixture was worked up as described above. Dimethyl tetrachlorosuccinate (**6**) was identified as the major reaction product by GLC (comparison with authentic sample).

**Reaction of methyl dibromoacetate (7) with benzaldehyde (2a).** A solution of ester **7** (0.30 g, 1 mmol), benzaldehyde **2a** (0.10 g, 1 mmol), and $Fe(CO)_5$ (0.39 g, 2 mmol) in HMPA (1 mL) was kept at –20 °C for 3 days. The reaction mixture was worked up as described above. Diastereomeric methyl 2-bromo-3-hydroxy-3-phenylpropionates (**8a**) were identified as the reaction products in a ratio of 1 : 1. The yield was 18%. $^1H$ NMR, δ*: 3.55 (s, 3 H, MeO); 4.45 (d, 1 H, CHBr, $J$ = 6 Hz); 4.65 (br.s, 1 H, OH); 5.05 (d, 1 H, CH, $J$ = 6 Hz); 7.20—7.60 (m, 5 H, Ph). MS, $m/z$ ($I_{rel}$ (%))*: 259 $[M + 1]^+$ (2), 241 $[M - OH]^+$ (24), 171 (28), 107 (25), 91 (100). Methyl cinnamate (the yield was 6%) and ester **3a** were also identified by GLC-mass spectrometry.

**Reaction of ester 7 with butyl methyl ketone (2b).** A solution of ester 7 (0.30 g, 1 mmol), ketone **2b** (0.10 g, 1 mmol), and $Fe(CO)_5$ (0.39 g, 2 mmol) in HMPA (1 mL) was kept at –20 °C for 3 days. The reaction mixture was worked up as described above. Methyl 2-bromo-3-hydroxy-3-methylheptanoate (**8b**) was identified as the major reaction product. The yield was 10%. $^1H$ NMR, δ: 4.22 (s, 1 H, CHBr); 3.83 (s, 3 H, MeO); 3.28 (br.s, 1 H, OH); 1.34 (s, 3 H, MeC); 1.10—1.40 (m, 6 H, 3 $CH_2$); 0.83 (t, 3 H, $\underline{Me}CH_2$). MS, $m/z$ ($I_{rel}$ (%)): 252 $[M]^{+\cdot}$ (1), 235 $[M - OH]^+$ (100), 195 (7), 155 (55), 101 (59).

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* The spectrum of one isomer is given.

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